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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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DRINKER BIDDLE & REATH (DC)
1500 K STREET, N.W.
SUITE 1100
WASHINGTON, DC 20005-1209

EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/402,093	OHSUYE ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-62,64-68,70-73,76 and 78-98* is/are pending in the application.

4a) Of the above claim(s) *84-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-62,64-68,70-73,76,78-81,94-96 and 98* is/are rejected.

7)☒ Claim(s) *82,83 and 97* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/25/07;9/15/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2007 has been entered.

The amendment filed on October 25, 2007 amending the specification to correct typographical errors, amending claims 54, 72, 96 and 97, canceling claims 63 and 69 has been entered.

A substitute Sequence Listing and the computer readable form thereof filed October 25, 2007 have been entered.

Claims 54-62, 64-68, 70-73, 76 and 78-98 are pending. Claims 84-93 have been previously withdrawn.

Information Disclosure Statement

The reference, Chinese patent application (CN 1167155), in the information disclosure statement filed September 15, 2003 is lined through because it fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is

not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Election/Restrictions

Applicants argue that "the Office incorrectly lists at least claims 78, 80, 81, and 93 as being withdrawn" (Remarks of 10/25/07, page 13). This is agreed with regard to claims 78, 80 and 81 that have been rejoined with the elected claims and examined. This is not agreed with regard to claim 93, which while "refers to SEQ ID NO:20" does not limit the scope to the elected fusion protein or peptide of interest. Therefore, claim 93 remains withdrawn.

Claim Objections

Claims 54-62, 64-68, 72, 73, 76, 78-81 and 98 are objected to because they fail to comply with the requirements of 37 CFR 1.821 through 1.825 for Patent Applications containing nucleotide sequence and/or amino acid sequence disclosures.

37 CFR 1.821(d) requires the use of assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences. Claim 54, with dependent claims 55-62, 64-68, 78-81, 98 and claim 72, with dependent claims 73 and 76, recite the sequences of the specific GLP-1 derivatives without reciting their sequence identifiers. The claims should be amended to recite SEQ ID NO: after each specific GLP-1 derivative. For example, GLP-1 (7-36) (SEQ ID NO:27), GLP-1 (7-37) (SEQ ID NO:28), etc.

Claim 97 is objected to because it recites the genera of protective peptides, helper peptides and peptides of interest, whereas the claim is limited to the specific sequences of SEQ ID NOs: 20-23 that contain the specific protective peptide, helper peptide and peptide of interest.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54-62, 64-68, 72, 73, 76, 78-81, 94-96 and 98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 54-62, 64-68, 72, 73, 76, 78-81, 94-96 and 98 are drawn to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide, a helper peptide and a peptide of interest, a vector and a cell comprising said DNA.

The claims encompass the genus of protective peptides and the genus of helper peptides. While the genus of protective peptides is represented by a single peptide that is a fragment of *E. coli* β-galactosidase, other protective peptides and their role in the

purification of a peptide of interest are known in the art. Furthermore, the protective peptides are auxiliary to the instant invention. However, the helper peptides are the crux of the invention. The highly variable genus of helper peptides is described by pI that should be between 8 and 12 when a helper peptide is connected to the peptide of interest. The representative species of said genus are limited to the helper peptides that are part of SEQ ID NOs: 20-23, wherein fusion proteins of SEQ ID NOs: 20 and 23 comprise the same helper peptide of 13 amino acids, SEQ ID NO: 22 comprises helper peptide of 13 amino acids that differs from the one in SEQ ID NOs: 20 and 23 by a single substitution and SEQ ID NO:21 comprises a 16 amino acids helper peptide that is highly homologous with the previous ones. The specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a protective or helper peptide and fails to provide any structure: function correlation present in all members of the claimed genus. The specification does not teach the production of any other peptide of interest. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of the species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 54-62, 64-68, 72, 73, 76, 78-81, 94-96 and 98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of making derivatives of human GLP-1 using fusion proteins shown at Figures

7, 11-13 (SEQ ID NOs: 20-23), does not reasonably provide enablement for a process of making a GLP-1 derivative recited in the claims using other helper peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 54-62, 64-68, 72, 73, 76, 78-81, 94-96 and 98 are directed to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide, a helper peptide and a specific peptide of interest, a vector and a cell comprising said DNA.

Therefore, they are drawn to a method of making of a genus of polypeptides of interest having the specific defined structures, wherein the isoelectric point of said peptide of interest connected to a helper peptide of any structure is between 8 and 12. While the specification teaches a method of making of a highly purified GLP-1 derivative using the specific construct comprising the specific helper peptide, it does not provide any guidance as to a process for producing a highly purified GLP-1 derivative using a helper peptide of an unknown structure. This would involve designing a helper peptide-peptide of interest fusion with the only limitation of having isoelectric point in the wide range of 8-12. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The claimed method encompasses purification of any peptide using a fusion of a peptide of interest and a helper peptide wherein the attachment of a helper peptide would change characteristics of the peptide of interest. This would involve

experimentation to find the helper peptide that being attached to the peptide of interest would change characteristics of the latter, so that it would become possible to use the fusion of protective peptide, helper peptide and peptide of interest in a claimed method.

The state of the art is such that it is unpredictable which helper peptides other than the ones present in fusion proteins of SEQ ID NOs: 20-23 should be used. The specification provides no guidance on the matter.

It is known in the art that the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable. Consequently, excessive trial and error experimentation would be required to identify the necessary helper sequence that would impart the properties allowing the production of a highly purified peptide of interest since the amino acid sequence of such a helper peptide useful with any peptide of interest could not be predicted *a priori*. The specification provides no guidance on predicting a helper of what structure would be suitable for a given peptide of interest. Furthermore, the development of an appropriate purification scheme for a peptide with known characteristics requires additional trial and error experimentation.

Therefore, one skilled in the art would require guidance as to how to make a highly purified peptide of a GLP-1 derivative recited in the claims using a helper peptide of any function and structure by a claimed process. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-62, 64-68, 70-73, 76, 78-81, 94-96 and 98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54-62, 64-68, 72, 73, 76, 78-81, 94-96 and 98 recite various positions in the sequence of the GLP-1 derivatives. Without the identified structure, said positions are not defined rendering the claims unclear.

Claims 70 and 71 are incomplete as dependent from canceled claim 69.

No art was found for SEQ ID NO:20. The search continued for SEQ ID NOs: 21-23 for which no art was found.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 72, 73 and 76 are rejected under 35 U.S.C. 102(e) as being anticipated by Suzuki et al.

Suzuki et al. (US Patent 5,891,671, form PTO-892 mailed May 312, 2007) teach an expression vector comprising a DNA encoding a fusion protein comprising the protective peptide, helper peptide and 7-37 GLP-1 and an *E. coli* transformed with said vector (columns 5 and 6, columns 17-20, Examples 11-14, claim 13). Said protective peptide is a fragment of *E. coli* β-galactosidase that is used in the instant invention and cleavage site between a linker peptide and a peptide of interest is a Kex2 protease cleavage site as in the instant invention. The bond between protective and linker peptides represents another cleavage site.

Absent evidence to the contrary the fusion of the helper peptide and the 7-37 GLP-1 fusion has the requisite pI. They further teach other peptides of interest such as GLP-1 (7-36) NH_2 that can be obtained similarly (e.g., column 5, line 22).

The applied reference has a common inventor, Yuji Suzuki, with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Allowable Subject Matter

Claims 82 and 83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

Applicant's arguments filed October 25, 2007 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph written description rejection, the rejection as related to protective peptides is withdrawn in view of Applicants arguments that protective peptides were known in the art at the time the invention was made (Remarks, page 15 and page 17). However, the rejection is maintained with regard to the description of the genus of helper peptides. The helper peptide is essential for the instant invention. Applicants argue that "Determination of the sequences for use as the helper peptide for any specific peptide of interest also would be readily determinable based on the pI of the peptide of interest. The fact that the genus of helper peptides is large does not vitiate the ability to determine helper peptides that would have a different but suitable pI. Determination of appropriate sequences would be easily determinable by use of software at the time. Thus, the structure and properties of the peptide of interest coupled with the function of the peptide if interest and guidance of how to select sufficiently describes the helper peptide" (page 18). This is not persuasive because the genus of helper peptides is not defined by structure but by a range for a single feature,

pI. While the pI of a given sequence can be determined, said sequence is not described. The entire highly variable genus is represented by 3 helper peptides of similar structure (SEQ ID NOs: 20 and 23 comprise the same helper peptide, *supra*).

With regard to the 112, 1st paragraph enablement rejection, Applicants argue that "knowing the pI of the peptide of interest and reading the specification regarding the helper peptide as discussed in section 7 above, the skilled artisan would have been able to make and use a large number of [helper peptide + peptide of interest] combinations with the appropriate pI. The parameters in the specification provide all the information necessary" (page 19). This is not agreed with because there is a countless number of peptides that consist of 5-50 amino acids and have the range of pI between 8 and 12. The specification provides no guidance as to which of them will be useful in the instant invention.

With regard of the 102(e) rejection, Applicants argue that "Suzuki does not teach or suggest the recited peptides of interest let alone the combination of fusion proteins presented herein. The '671 patent at best teaches a fusion protein comprising [protective peptide]-[linker site]-[peptide of interest]. Applicants' claims are directed to a fusion protein generally described as [protective peptide]-[helper peptide]-[peptide of interest]. No linker site is recited in the composition of the pending claims. Additionally, '671 patent does not teach or suggest the use of a helper peptide, let alone the order provided" (page 21). This is not persuasive because, Suzuki teach a peptide of interest, 7-37 GLP-1, and the "linker site" is construed as a helper peptide because its length is within required 5-50 amino acids and pI, absent evidence to the contrary, is within 8-12

(columns 17-20, Examples 11-14 and Figures 14-15). Applicants further argue that "the example of the '671 patent provides for cleavage of the fusion protein by a Kex2 protease. However, there is no cleavage site between the [protective peptide] and the [linker site]" (page 21). This is not persuasive because a peptide bond between the protective peptide and the linker can be cleaved by some agent, either a protease or a chemical agent, and therefore, is a cleavage site.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

January 14, 2008